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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/644,579	08/20/2003	Connie Sanchez	05432/100M919-US1	5200

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EXAMINER	
CHONG, YONG SOO	
ART UNIT	PAPER NUMBER
1617	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/644,579	SANCHEZ ET AL.	
	Examiner	Art Unit	
	YONG S. CHONG	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/16/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/1/2008 has been entered.

Claim(s) 1-19, 41-44 have been cancelled. Claim(s) 20-40 are pending. Claim(s) 20 has been amended. Claim(s) 20-40 are examined herein.

Applicant's arguments have been fully considered but found not persuasive. The rejections of the last Office Action are maintained for reasons of record and modified below as a result of the new claim amendments. The following new double patenting rejections will also apply.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 20-40 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 20, 22-37 of copending Application No. 10/644,588; claims 43, 45, 47 of copending Application No. 11/020,632; claims 1-5, 9-11, 18 of copending Application No. 11/539,100; and claims 20-31 of copending Application No. 11/853,949 in view of applicant's own admission.

Applications 10/644,588, 11/020,632, 11/539,100, and 11/853,949 discloses a method of treating depression in a patient who is being administered the selective serotonin reuptake inhibitor, escitalopram. The applications do not disclose a patient population who has failed to respond to initial treatment with citalopram.

In applicant's own admission, the specification discloses that clinical studies on depression and anxiety disorders indicate that non-response or resistance to SSRIs, such as citalopram, where at least 40-60% reduction in symptoms has not been achieved during the first 6 weeks of treatment (pg. 1, paragraphs 2-3). The specification also states that substantially all of the antidepressant effect is in the S-enantiomer, which is escitalopram, of the racemate, citalopram (pg. 2, paragraph 1).

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed invention was made, to administer escitalopram to a patient who failed to respond to the initial treatment with citalopram.

A person of ordinary skill in the art would have been motivated to administer escitalopram because of the reasonable expectancy of successfully optimizing a treatment for depression using a more effective selective serotonin reuptake inhibitor.

This is a provisional obviousness-type double patenting rejection.

Response to Arguments

The double patenting rejections over Applications 10/468,685 and 10/644,587 have been withdrawn because they have been abandoned.

Applicant's request that provisional rejection over Application 10/644,588 be held in abeyance is acknowledged. The double patenting rejection is maintained for reasons of record.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham vs John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 20-40 are rejected under 35 U.S.C. 103(a) as being obvious over Boegesoe et al. (US Patent 4,943,590) in view of applicant's own admission.

The instant claims are directed to a method of treating depression in a patient, who failed to respond to initial treatment with the selective serotonin reuptake inhibitor, citalopram, by administering a pharmaceutically effective amount of escitalopram.

Boegesoe et al. discloses the method of treating depression in a patient with the (+) enantiomeric form of citalopram, otherwise referred to as escitalopram (col. 1, lines 9-26), which is also disclosed to be an inhibitor of serotonin uptake. Acceptable pharmaceutical salts of escitalopram include oxalate (col. 1, lines 29-42). The daily dosage of escitalopram is disclosed to be from 5 to 50 mg (col. 8, lines 55-60). Boegesoe et al. teach that while citalopram is a well-known antidepressant in man (col. 1, lines 65-67), substantially all of the antidepressant activity (5-HT uptake inhibition) resides in the (+)-enantiomer, escitalopram (col. 2, lines 38-40).

However, Boegesoe et al. fail to disclose specifically the patient population that consists of those who failed to respond to the initial treatment with the selective serotonin reuptake inhibitor, citalopram.

In applicant's own admission, the specification discloses that clinical studies on depression and anxiety disorders indicate that non-response or resistance to SSRIs, such as citalopram, where at least 40-60% reduction in symptoms has not been achieved during the first 6 weeks of treatment (pg. 1, paragraphs 2-3).

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed invention was made, to administer escitalopram to a patient who failed to respond to the initial treatment with the selective serotonin reuptake inhibitor, citalopram.

A person of ordinary skill in the art would have been motivated to administer escitalopram to a patient who failed to respond to the initial treatment with the selective serotonin reuptake inhibitor, citalopram, because: (1) citalopram is a well-known antidepressant in man; (2) it is also a well-known fact that there is a non-response or resistance to SSRIs, where at least 40-60% reduction in symptoms has not been achieved during the first 6 weeks of treatment for depression; (3) and that substantially all of the antidepressant activity resides in the (+)-enantiomer, escitalopram. Therefore, the skilled artisan would have had a reasonable expectation of success in treating depression in a patient who failed to respond to the initial treatment with the selective serotonin reuptake inhibitor, citalopram, by administering escitalopram.

Examiner respectfully points out that the limitation directed to an amount "to obtain an effect in a patient after one week," has been inherently met as a result of meeting the limitations with respect to drug, dosage, and patient population.

Response to Arguments

Applicant argues unexpected results in the form of the clinical study performed by D.L. Zimbroff et al. (presented at CINP2004) and abstract of Int. J. Neuropsychopharm. 7(S1):S348, P02.164 (June 2004). Specifically, it was found that

the remission rate for patients treated with escitalopram after unsuccessful treatment with citalopram was 37% and 42%. Thus, patients who did not respond to initial treatment with citalopram surprisingly responded and even reached remission when treated with escitalopram.

Although Applicant still insist the Zimbroff abstract should be considered even though it was published after the effective filing date of the claimed invention, it is still not persuasive because there is no clear showing of unexpected results. Applicant has assumed that the efficacy of escitalopram when compared to citalopram is unexpected. However, Applicant is wrong to assume this because there is nothing unexpected or surprising about this. Specifically, it was known in the art prior to the claimed invention that substantially all of the antidepressant activity resides in the (+)-enantiomer, escitalopram. Therefore, one of ordinary skill in the art would have had a reasonable expectation of success in treating depression with escitalopram over citalopram.

Regarding the establishment of unexpected results or synergism, a few notable principles are well settled. The Applicant has the initial burden to explain any proffered data and establish how any results therein should be taken to be unexpected and significant. See MPEP 716.02 (b). It is applicant's burden to present clear and convincing factual evidence of nonobviousness or unexpected results, i.e., side-by-side comparison with the closest prior art in support of nonobviousness for the instant claimed invention over the prior art. The claims must be commensurate in the scope with any evidence of unexpected results. See MPEP 716.02 (d). With regard to synergism, a prima facie case of synergism has not been established if the data or

result is not obvious. The synergism should be sufficient to overcome the obviousness, but must also be commensurate with the scope of the claims. Further, if the Applicant provides a DECLARATION UNDER 37 CFR 1.132, it must compare the claimed subject matter with the closest prior art in order to be effective to rebut a prima facie case if obviousness. See MPEP 716.02 (e).

Applicant argues that it was the inventors that surprisingly discovered that the R-enantiomer in citalopram has a negative effect on citalopram resulting in citalopram's inferior efficacy. None of the cited references discloses or suggests the detrimental influence of the R-enantiomer, or that administration of escitalopram alone would provide the demonstrated superior therapeutic effect over racemic citalopram.

This is not persuasive because Boegesoe clearly teaches that escitalopram substantially possesses all the antidepressant activity. Therefore, the motivation to administer escitalopram over racemic citalopram is obvious and need not address Applicant's arguments regarding the detrimental influence of the R-enantiomer.

"The reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant." >See, e.g., *In re Kahn*, 441 F.3d 977, 987, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006) (motivation question arises in the context of the general problem confronting the inventor rather than the specific problem solved by the invention); Cross Med. Prods., Inc. v. Medtronic Sofamor Danek, Inc., 424 F.3d 1293, 1323, 76 USPQ2d 1662, 1685 (Fed. Cir. 2005) ("One of ordinary skill in the art need not

see the identical problem addressed in a prior art reference to be motivated to apply its teachings.");< *In re Linter*, 458 F.2d 1013, 173 USPQ 560 (CCPA 1972) (discussed below); *In re Dillon*, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1990), cert. denied, 500 U.S. 904 (1991) See MPEP 2144.

Applicant argues that one of ordinary skill in the art would not have expected escitalopram to have different efficacy than citalopram. At best, one of ordinary skill would have expected escitalopram to provide increased potency - i.e. achieving the same response in the patient, but requiring only half the dose to do so.

This is not persuasive because Applicant is assuming that (-)-citalopram has no effect on the activity of escitalopram. As Applicant has generously pointed out in the form of Exhibit A and B, it is generally unpredictable to assume which enantiomer has the beneficial effect or even a detrimental effect if at all.

Applicant also argues that the unpredictability of individual enantiomers is well known in the art. The beneficial effects may reside in the racemic form or in one of its individual enantiomers. Therefore, there is no way to predict the beneficial activity based on the structure, nor what type of activity is actually involved. Applicant provides fluoxetine (Prozac) as a demonstration of such unpredictability.

This is not persuasive because while this may be generally true, it does not apply to this specific case since it was known prior to Applicant's claimed invention, which enantiomer possesses the beneficial activity. Applicant is again assuming that escitalopram was not known to have substantially all the antidepressant activity as

taught by Boegesoe. Furthermore, the arguments directed to fluoxetine (Prozac) are irrelevant to this case.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong S. Chong whose telephone number is (571)-272-8513. The examiner can normally be reached on M-F, 9-6.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, SREENI PADMANABHAN can be reached on (571)-272-0629. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Yong S Chong/
Examiner, Art Unit 1617

YSC